wall, and the intervening fascia. This makes it virtually certain that the placenta will not be detected before it is separated and serious bleeding provoked.

Early Detection of Pre-eclampsia

Early detection of pre-eclampsia is a *sine qua non* of good antenatal care. Traditional obstetric teaching is that there is an aetiological relationship between abruptio placentae and pre-eclampsia, and it is implied that toxaemia predisposes to abruption. If this is true, early detection of pre-eclampsia followed by appropriate management of the toxaemic process might be expected to result in a reduction in the incidence of abruption. It is remarkable, however, how infrequently abruption is seen in patients in whom a prior diagnosis of pre-eclampsia has been made, and recently the existence of a significant aetiological relationship has been seriously questioned.[4]

Avoidance of Trauma

The one specific form of trauma in the antenatal period which may account for some cases of ante-partum haemorrhage is that produced by external version. Opinion varies widely with regard to the place of external version in modern obstetrics, but most obstetricians agree that if it has any place it should only be attempted gently on unanaesthetized patients. If the manipulations prove difficult or cause pain, the attempt should be abandoned immediately.

Avoidance of Sudden Uterine Decompression

A rare cause of abruptio placentae is the sudden release of liquor amnii in cases of severe polyhydramnios. The sudden reduction in the area of the uterine wall to which the placenta is attached may result in placental separation in a manner similar to that which occurs in the third stage of normal labour after the baby has been expelled.

[*To be concluded.*]

REFERENCES

1 O'Sullivan, J. F., *J. Obstet. Gynaec. Brit. Cwlth*, 1963, **70**, 158.
2 Ministry of Health, *Report on Confidential Enquiries into Maternal Deaths in England and Wales 1958–60*, 1963. H.M.S.O., London.
3 Hibbard, E. D., *J. Obstet. Gynaec. Brit. Cwlth*, 1962, **69**, 739.
4 Hibbard, B. M., ibid., 1962, **69**, 282.

TO-DAY'S DRUGS

Cough Suppressants

The traditional cough mixture is still one of the commonest medicines prescribed. Surveys of prescribing habits indicate that such mixtures account for 8 to 10% of all prescriptions issued on Form E.C.10.[1] If one adds to this the number of cough remedies which are bought over the counter without prescriptions the annual expenditure on such medicines must be enormous. The majority of these medicines are prescribed or bought with the intention that they will alleviate cough by preventing it, and most cough mixtures contain at least one drug which is recognized as a cough suppressant. Many of them also contain other drugs which are claimed to act as expectorants, decongestants, or bronchodilators. The pharmacological activity of these ingredients in the doses in which they are present in most cough mixtures is usually negligible and the real value of such nostrums is due either to a placebo effect or to the pharmacological action of the antitussive drugs which they contain.

Pharmacology

Cough is a protective physiological reflex whose purpose is to keep the respiratory tract free from particulate matter and accumulated secretions. The reflex is usually initiated by noxious agents irritating some part of the mucous membrane of the respiratory tract. The cough centre is situated in the medulla adjacent to the roots of the vagus and glossopharyngeal nerves. The cough reflex is to a large extent under voluntary control, so that coughing can be voluntarily suppressed; and conversely it can be centrally originated. A cough suppressant can be defined as a drug which raises the threshold of the cough centre, or acts peripherally in the respiratory tract to reduce the impulses which pass to this centre; or combines both these actions.[2]

The assessment of cough suppressants is difficult. It is possible to induce cough experimentally both in animals and in man, for example by the inhalation of an aerosol containing either acetylcholine or citric acid, and many drugs have proved effective antitussive agents when tested for their ability to reduce the amount of coughing after a standard cough-inducing stimulus has been given. The results obtained by such methods, however, do not always correlate well with the clinical effectiveness of the drug in the treatment of pathological cough in man. There is no reliable way of assessing the value of a cough suppressant except by clinical trials in patients with respiratory disease. Unfortunately, there have been very few studies in which antitussive drugs have been adequately tested by suitably designed controlled trials using either a placebo or a well-established remedy as a standard for comparison. In most trials many of the patients have been suffering from acute respiratory infections which are self-limiting and in which the duration of cough is short. Moreover it has been shown that in the majority of such patients cough can be relieved by a simple syrup which does not contain any active drug.[3] In most trials also the assessment is made of the patients' own impression of the effectiveness of the treatment. Even when patients claim subjective benefit and consistently recognize one drug as better than another this does not necessarily mean that the drug has reduced the amount of coughing.[4] Very recently an ingenious method of measuring the amount of coughing objectively by means of a tape-recorder system has been described.[5] By this method it has been shown that most patients with chronic cough have little idea of the extent to which their cough varies from day to day, and that they are usually unaware of the effects of antitussive drugs. Most cough suppressants also have sedative, analgesic, or euphorigenic properties, and it may be that their clinical value is due to these actions rather than to any specific antitussive effect.

Cough-suppressant Drugs

The traditional cough-suppressant drugs are derivatives of opium. There are a number of official, well-established mixtures which contain relatively small amounts of opium alkaloids (Table I). These well-tried remedies should not be neglected in favour of newer and more exotic preparations,

because there is little evidence that the new drugs have any great superiority.

TABLE I.—*Official Cough Mixtures Containing Opium Alkaloids*

Preparation	Dose (ml.)
Camphorated opium compound mixture (*B.P.C., B.N.F.*)	15–30
Codeine linctus (*B.P.C., B.N.F.*)	2–4
Diamorphine linctus (*B.P.C.*)	2–8
Noscapine linctus (*B.P.C., B.N.F.*)	5
Squill opiate linctus (*B.P.C., B.N.F.*)	2–4
Syrup of codeine phosphate (*B.P.C.*)	2–8

Of individual drugs **codeine** is probably that which is prescribed most frequently. It is preferred to morphine because it does not depress respiration so much, because side-effects such as nausea, vomiting, and constipation are less common, and because addiction, though it may occur, is rare. When it is given for the relief of cough codeine is usually prescribed either as codeine linctus or as syrup of codeine phosphate, but it is also effective in tablet form, and for the treatment of chronic cough tablets are preferable. Opinions vary on the dose of codeine required to suppress cough. Some consider that a dose of 60 mg. of codeine phosphate should be given three or four times daily,[6] whereas others advocate a dose of 15 mg. or 4 ml. of syrup of codeine phosphate every two hours.[7] Many proprietary cough mixtures contain codeine as their main active ingredient, but there is no evidence that any of these are better than the official preparations, and the amount of codeine contained in the recommended dose of many of them is less than the doses mentioned above as being necessary for the prevention of cough.

Dihydrocodeine and **dihydrocodeinone** are both pharmacologically more active than codeine. Dihydrocodeinone is recognized as a drug of addiction, and instances of young people becoming addicted to cough mixtures containing dihydrocodeinone have been reported.[8] A long-acting preparation in which dihydrocodeinone and the antihistamine phenyltoxolamine are combined in a sulphonic resin complex has recently been advocated for the treatment of chronic cough, particularly for the suppression of night cough.[2 9] However, the advisability of using a known addictive drug in any form in a chronic condition is clearly open to question.

Many physicians believe that the best drug in cases of pulmonary neoplasm and other inevitably fatal conditions accompanied by painful or distressing cough is **diamorphine hydrochloride** (heroin) and it is mainly for this that the drug is still prescribed in Great Britain. The usual dose is 6 mg. and it is usually better to give it orally as 8 ml. of the linctus of diamorphine than as a hypodermic injection. The danger of addiction is great, however, and unless it is certain that the patient's expectation of life is short some other drug should be preferred.

Noscapine (narcotine) is another naturally occurring opium alkaloid which is used for the suppression of cough. It is more closely related to papaverine than to morphine and has none of the side-effects nor the danger of addiction which are associated with the latter. As a cough-suppressant its activity is similar to that of codeine. The dose is 15–30 mg. and it is usually prescribed in the form of noscapine linctus (*B.N.F.*), which contains 15 mg. in 5 ml. It is also available as a tablet ("coscotabs," 25 mg. in each tablet).

In recent years the synthetic drug **pholcodine** has become as popular as codeine as a cough suppressant. Clinical trials have shown that it is at least as effective as codeine and diamorphine.[6 10] It has few toxic symptoms and does not cause euphoria, so that addiction is uncommon. The official preparations are pholcodine linctus (*B.N.F.*) and pholcodine linctus, strong (*B.N.F.*). The latter contains 10 mg. of pholcodine in 5 ml. and the official B.P. dose is 5–15 mg.; pholcodine linctus contains equal parts of the strong preparation and simple syrup. There are a large number of proprietary mixtures which contain pholcodine, but, as with codeine, the amount of pholcodine in the recommended dose is often less than the pharmacopoeial dose.

Methadone is another narcotic cough suppressant; its antitussive effect is similar to that of diamorphine and it is also an analgesic, but it depresses respiration and therefore should be used with caution in many respiratory diseases, especially in children. It is a drug of addiction and should be given for short periods only. The dose is 2–5 mg., given either as methadone linctus (*B.N.F.*) or in tablet form.

Dextromethorphan is a synthetic morphine derivative which has little or no narcotic action and is not an analgesic. Its toxicity is low, it causes few side-effects, and does not give rise to addiction. Opinions vary about its efficacy as a cough suppressant; in one trial it was shown to be approximately equivalent, milligramme for milligramme, to codeine,[11] but Beecher[4] found that, whereas patients could consistently recognize codeine and diamorphine as effective drugs when compared with a placebo, they could not do so with dextromethorphan. The official preparation is dextromethorphan tablets (*B.P.*), but the drug is also available in proprietary form as a syrup. The dose is 15–30 mg.

Caramiphen is a drug with atropine-like activity. The hydrochloride ("parpanit") is used for the treatment of Parkinsonism and the **ethanedisulphonate** ("taoryl") is a centrally acting cough-suppressant. In clinical trials it has proved less active than an equal dose of codeine.[12] The side-effects are slight nausea, dizziness, and occasional drowsiness. The drug does not appear to have any special advantages and it is therefore difficult to understand why it has been included in the new (1963) edition of the *National Formulary* in preference to some of the other new antitussive drugs. The dose is 10–20 mg.

In addition to these official preparations there are a large number of recently introduced proprietary cough remedies, some of which are listed in Table II. Few of these have been subjected to adequate clinical trials. Even those which have been so tested have not been shown to be superior to older and well-established drugs. Among newer remedies **benzonatate** calls for special mention because its mode of action is thought to differ from that of other antitussive drugs. It is chemically related to local anaesthetics and is believed to have a selective action on the pulmonary stretch receptors. It has also been shown to act centrally by inhibiting spinal reflexes and also by affecting the transmission of impulses in the vagal nuclei in the medulla. Benzonatate is claimed to be of particular value in cases where cough is associated with bronchospasm, but it is ineffective when cough is due to bronchoscopy, when it occurs post-operatively after thoracotomy, and in cough due to pulmonary congestion. Clinical studies have been largely uncontrolled, and at best it can be said that the antitussive effect of 100 mg. of benzonatate is similar to that of 15 mg. of codeine. Side-effects are

TABLE II.—*New Non-official Cough Suppressants*

Official Name	Proprietary Name	Presentation	Dose (mg.)
Benzonatate	Tessalon	Capsules	100
Carbetapentane	Toclase	Syrup; Tablets	15–30
Chlorphedianol	Detigon	Liquid; Linctus	25
Dimethoxanate	Thorpax	Syrup	25–50
Isoaminile	Dimyril	Liquid; Capsules	20–60
Levopropoxyphene	Letusin	Capsules; Liquid	100
Oxeladin	Pectamol	Linctus	10–20
Pipazethate	Selvigon	Syrup; Tablets	20–40
Piperidione	Sedulon	Syrup	100
Sodium dibunate	Becantyl	Syrup; Tablets	20–30

uncommon, but drowsiness, nausea, pruritus, nasal congestion, and vertigo have been recorded.

Conclusion

In the great majority of cases cough is due to an acute, self-limiting upper respiratory infection. In such cases the use of a simple demulcent preparation such as simple linctus (*B.P.C., B.N.F.*) is usually all that is required to give symptomatic relief. If something more than this is required the well-established official preparations should be perfectly adequate, and there is at present no good reason for recommending any of the newer, more elegant, and usually more expensive drugs. When it is thought desirable to attempt to suppress a chronic cough one of the non-narcotic and non-addicting drugs is to be preferred, but it has not been shown conclusively that pholcodine, noscapine, or dextromethorphan has any advantage over codeine. Only in cases of terminal illness with distressing cough should addictive drugs such as diamorphine and dihydrocodeinone be used.

REFERENCES

1 Dunlop, D. M., Inch, R. S., and Paul, J., *Brit. med. J.*, 1953, **1**, 694.
2 Bickerman, H. A., *Med. Clin. N. Amer.*, 1961, **45**, 805.
3 Boyd, E. M., *Lancet*, 1946, **2**, 735.
4 Beecher, H. K., *Measurement of Subjective Responses*, 1959, p. 399. Oxford University Press, London.
5 Woolf, C. R., and Rosenberg, A., *Thorax*, 1964, **19**, 125.
6 Alstead, S., *Clinical Pharmacology*, 20th ed., 1960, p. 336. Cassell, London.
7 Bickerman, H. A., in *Drugs of Choice 1960-61*, 1960, edited by W. Modell, p. 493. Kimpton, London.
8 Rosenwald, R. J., and Russell, D. H., *New Engl. J. Med.*, 1961, **264**, 927.
9 Cass, L. J., and Frederik, W. S., *Ann. intern. Med.*, 1958, **49**, 151.
10 Snell, E. S., and Armitage, P., *Lancet*, 1957, **1**, 860.
11 Cass, L. J., Frederik, W. S., and Andosca, J. B., *Amer. J. med. Sci.*, 1954, **227**, 291.
12 Bickerman, H. A., *Clin. Pharmacol. Ther.*, 1962, **3**, 353.

ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

External Cephalic Version

Q.—*Is external cephalic version still advocated as a treatment for a breech presentation? If so, when should it be attempted and should it be persisted with to the extent of giving a general anaesthetic to achieve it?*

A.—Breech presentation is known to carry an increased risk to the foetus, and for this reason external version is recommended in most cases. Nevertheless, it must be remembered that the operation itself is not without risk to the foetus. The chief dangers are that the placenta may be separated, that premature labour may ensue, or that the cord may become wound round the foetus.

Each case must be considered on its merits. External version should not be performed in multiple pregnancy, in cases of severe toxaemia, in cases where there is a scar in the uterus, in cases of severely contracted pelvis, or in cases of congenital malformation of the uterus. It is undesirable in the presence of severe foetal malformation, such as a major degree of hydrocephalus, or if the foetus is dead. It is also best avoided in any case where there has been bleeding during pregnancy.

The question of when version is best performed is controversial, but it may be attempted at any time after the 32nd week in a primigravida and after the 34th week in a multipara. This is a rule of thumb, aimed at finding the best time for version, bearing in mind that spontaneous version may occur if nothing is done.

Modern obstetric opinion does not favour the use of general anaesthesia for version, though premedication with pethidine and promazine or with "omnopon" and scopolamine may help a nervous patient. If a general anaesthetic is used it is important to use the utmost gentleness in turning the baby, as the use of anaesthetic has been shown to increase the risk of premature labour.

External version is most useful in a young primigravida with borderline pelvic measurements. When version fails there is little alternative to caesarean section if the baby is to be delivered with maximum safety, but external version to a cephalic presentation permits a trial of labour.

Sterility After Mumps Orchitis

Q.—*What is the approximate incidence of sterility in the male after orchitis? Is there any regeneration of fertility after initial sterility in this condition? Is there any increased risk of an abnormal foetus in the child of a father who has had orchitis?*

A.—It is difficult to ascertain the incidence of sterility after mumps orchitis. Data are available only in relation to men who have been investigated for infertility, and we do not know, for example, how many husbands whose wives have conceived have had mumps orchitis. Nevertheless it is fairly clear from data relating to men complaining of infertility that the incidence is high. Thus Bayle and Gouygou[1] found all of 15 cases who had had bilateral orchitis to be azoospermic, while in 20 cases said to have had only unilateral orchitis 9 were also azoospermic, the remaining 11 being oligospermic. Bayle and Gouygou mention a further 8 cases with either azoospermia or oligospermia in which, although mumps had occurred after puberty, orchitis had not been noticed by the patients.

The mumps virus damages primarily the germinal epithelium, but also to a varying extent the rest of the testicular tissue. When there is severe atrophy almost the whole testis may be replaced by scar tissue. The damage is irreversible and when sterility results it is permanent and not susceptible to treatment.

I do not believe there is any evidence that mumps orchitis in the father is likely to increase the incidence of foetal abnormalities in his subsequent offspring.

REFERENCE

1 Bayle, H., and Gouygou, C., *La Stérilité Masculine*, 1953. Association Française d'Urologie, Paris.

Lysine-vasopressin Nasal Spray

Q.—*Is there a preparation of pituitary (posterior lobe) for insufflation which is not in powdered form as snuff? A patient has diabetes insipidus and asthma and is allergic to pitressin snuff. Injections of vasopressin tannate are satisfactory but inconvenient, and a non-injectable preparation would be much preferable.*

A.—There has recently been introduced a preparation of synthetic lysine-vasopressin which is administered in the form of a nasal spray. It is claimed that this preparation has the following advantages: simplicity of treatment, avoiding the need for frequent injections; a single synthetic active substance of uniform potency; and complete freedom from animal protein and thus from allergic reactions. Preliminary reports on its use[1,2] indicate that complete control can be achieved with it in cases of diabetes insipidus of moderate severity and partial control in severe cases. The usual dose is two sniffs up each nostril, and this has to be repeated every 3 to 5 hours. The drug is supplied in 5-ml. phials, each ml. containing 50 international units. A phial will last from 2 to 7 days. Of 16 patients mentioned in these preliminary reports one was unable to continue the treatment because of nasal congestion and ulceration of the nasal mucosa.

REFERENCES

1 Fraser, R., and Scott, D. J., *Lancet*, 1963, **1**, 1159.
2 Sjöberg, H., and Luft, R., ibid., 1963, **1**, 1159.

Detecting Phenothiazines in Urine

Q.—*Can the presence of phenothiazine drugs or their end products be detected in the urine? Are the tests reliable and can they be used quantitatively as well as qualitatively as a check on whether patients are taking the prescribed dose?*

A.—Relatively simple colorimetric tests for the detection in the urine of the metabolites of most of the commonly used phenothiazine drugs are available.[1-7] There is one test which will detect the presence in the urine of the metabolites of any phenothiazine compound and other more specific tests which